

## Jensen, Kathleen

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**From:** Zahner, Holly [Holly.Zahner@fda.hhs.gov]  
**Sent:** Tuesday, May 14, 2013 1:55 PM  
**To:** Jensen, Kathleen; Ankley, Gerald  
**Subject:** RE: Statistical Results of FHM Trenbolone study

Hi Gary and Kathleen,

Some of us will be working from home tomorrow, so please use the call in number below:

Call in number: 888-566-7603

Passcode: 61550

Talk you tomorrow at 11 am,  
Holly

### Holly M. Zahner, Ph.D.

Environmental Safety Team, HFV-162  
Office of New Animal Drug Evaluation  
Center for Veterinary Medicine  
U.S. Food & Drug Administration  
7500 Standish Place  
Rockville, MD 20855

Office: 240-276-8181

e-mail: [holly.zahner@fda.hhs.gov](mailto:holly.zahner@fda.hhs.gov)

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**From:** Jensen, Kathleen [mailto:Jensen.Kathleen@epa.gov]  
**Sent:** Wednesday, May 08, 2013 3:24 PM  
**To:** Zahner, Holly; Ankley, Gerald  
**Cc:** Silberhorn, Eric; Taylor, Veronica  
**Subject:** RE: Statistical Results of FHM Trenbolone study

Sounds good...thank you!

Kathy

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**From:** Zahner, Holly [<mailto:Holly.Zahner@fda.hhs.gov>]  
**Sent:** Wednesday, May 08, 2013 1:55 PM  
**To:** Jensen, Kathleen; Ankley, Gerald  
**Cc:** Silberhorn, Eric; Taylor, Veronica  
**Subject:** RE: Statistical Results of FHM Trenbolone study

Hi Kathleen,

No problem! We will talk to you and Gary on Wednesday at 11 am.

Some of us will be working from home that day, so I will provide a call in number later this week!

Holly

**Holly M. Zahner, Ph.D.**

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**From:** Jensen, Kathleen [<mailto:Jensen.Kathleen@epa.gov>]

**Sent:** Wednesday, May 08, 2013 11:00 AM

**To:** Zahner, Holly; Ankley, Gerald

**Cc:** Silberhorn, Eric; Taylor, Veronica

**Subject:** RE: Statistical Results of FHM Trenbolone study

Hi Holly,

I would like to propose delaying the call until Wednesday as I have to be out in the field on Tuesday. Will the same time (11:00 EST) on Wednesday work for you?

I apologize for the inconvenience.

Kathy

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**From:** Zahner, Holly [<mailto:Holly.Zahner@fda.hhs.gov>]

**Sent:** Tuesday, May 07, 2013 10:28 AM

**To:** Ankley, Gerald; Jensen, Kathleen

**Cc:** Silberhorn, Eric; Taylor, Veronica

**Subject:** RE: Statistical Results of FHM Trenbolone study

Great, we will talk to you next Tuesday!

Holly

**Holly M. Zahner, Ph.D.**

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**From:** Ankley, Gerald [<mailto:Ankley.Gerald@epa.gov>]

**Sent:** Tuesday, May 07, 2013 10:58 AM

**To:** Zahner, Holly; Jensen, Kathleen

**Cc:** Silberhorn, Eric; Taylor, Veronica  
**Subject:** RE: Statistical Results of FHM Trenbolone study

Looks OK for me—you can call Kathy and I at (218) 529-5147.

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**From:** Zahner, Holly [<mailto:Holly.Zahner@fda.hhs.gov>]  
**Sent:** Tuesday, May 07, 2013 9:53 AM  
**To:** Ankley, Gerald; Jensen, Kathleen  
**Cc:** Silberhorn, Eric; Taylor, Veronica  
**Subject:** RE: Statistical Results of FHM Trenbolone study

Hi Gary and Kathleen,

Thanks for fitting us in on such short notice. How is 11 am EST next Tuesday?

**Holly M. Zahner, Ph.D.**  
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**From:** Ankley, Gerald [<mailto:Ankley.Gerald@epa.gov>]  
**Sent:** Tuesday, May 07, 2013 8:06 AM  
**To:** Zahner, Holly; Jensen, Kathleen  
**Cc:** Silberhorn, Eric; Taylor, Veronica  
**Subject:** RE: Statistical Results of FHM Trenbolone study

Holly,

The next few days looks pretty booked—just learned this morning that I have about 10 hours of unanticipated EDSP-oriented conference calls today through Monday. Perhaps something next Tuesday (May 14) mid-morning would work for all of you?

Gary

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**From:** Zahner, Holly [<mailto:Holly.Zahner@fda.hhs.gov>]  
**Sent:** Monday, May 06, 2013 1:36 PM  
**To:** Ankley, Gerald; Jensen, Kathleen  
**Cc:** Silberhorn, Eric; Taylor, Veronica  
**Subject:** Statistical Results of FHM Trenbolone study

Hi Gary and Kathleen,

First, I wanted to say thank you again for providing a copy of the tabulated effects data from the trenbolone fish reproduction study. We have recently finalized our statistical analysis of the fish data you sent us in February. I attached two documents to this email that summarize our results and the statistical methods used.

Our Biostatisticians used three methods to determine a NOEC, EC5, EC10 and EC20 for the fecundity data only, including: 1) the statistical methods recommended in Annex 8 of OECD Guideline 229 to determine a NOEC, 2) the Poisson method to determine a NOEC, and 3) a marginal negative binomial regression model to determine the ECx values. We determined these effects values for the last 14 days of the study and the full 21 days of the study, which resulted in very different values. Based on the study design (1 male:1 female per rep) and the potential implications on the initial breeding, we decided to use the results from the last 14 days of the study. These data were found to be monotonic and the ECx values were more reliable. The 21 day data resulted in a non-monotonic response and ECx values are not reliable because the linear regression was not different from zero.

After internal discussions, we have decided to use the NOEC determined using the OECD method (for the last 14 days of egg production) because this is a universal method that is generally accepted around the world. The OECD method resulted in a NOEC of 32 ng/L for the last 14 days of the exposure period. With a safety factor of 10, our predicted no effects concentration (PNEC) that will be compared to the exposure assessment will be 3.2 ng/L, which is equivalent to an EC5 based on the linear regression analysis. However, in the published EA, we plan to include all statistical methods used and all values obtained using those methods to allow the public to see all the available information.

There are a few additional questions we had for you (listed below) and was wondering if you have time to talk this week or next week?

Questions:

- 1) The linear regression analysis determined an EC5, EC10, and EC20 of 3.1, 6.2, and 13.3 ng/L, respectively. This is very different from the EC50 of 11 ng/L reported in the publication. Could you provide us additional information on what method you used to estimate the EC50?
- 2) Do you have any comments on the methods we used and our results? We want to make sure to represent your data accurately and would appreciate any additional input that you have on the statistical results we have obtained.

Please let me know if there are specific day and times that work well for you!

We look forward to talking to you soon,  
Holly

**Holly M. Zahner, Ph.D.**

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